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Expert Opinion

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Becaplermin: recombinant platelet derived growth factor, a new treatment for healing diabetic foot ulcers

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Chronic or non-healing lower extremity ulcerations in diabetics are a significant cause of morbidity and mortality, and account for a large proportion of the financial burden related to the care of diabetics. Lower extremity ulcerations develop primarily as a consequence of neuropathy and the goal in addressing any wound is to re-establish tissue integrity as soon as possible. The healing of wounds is a complex procedure involving multiple growth factors, some of which have multiple effects on different cell types, in particular, platelet derived growth factor (PDGF) is a prominent agent, active in all stages of the healing process. Becaplermin (0.01% Regranex® gel) is a homodimeric protein produced by recombinant DNA technology through the insertion of the gene for the B chain PDGF into the yeast *Saccharomyces cerevisiae*. The biological activity of becaplermin is similar to that of indigenous PDGF-BB, specifically, the promotion of chemotactic recruitment and the proliferation of cells involved in wound repair. Becaplermin has undergone extensive animal and human studies, demonstrating that it is highly effective as an adjunctive measure for the healing of ulcerations in the feet of diabetics when used in conjunction with standard wound healing practices. Specifically these practices include the provision of a moist environment fr e of debris and necrotic tissue, control of infection and optimal weight displacement from the affected area. Becaplermin is safe and easy to use, being applied once-daily and at present, becaplermin is the only growth factor licensed for use in wound healing.

Keywords: becaplermin, diabetic foot ulcer, recombinant platelet derived growth factor, Regranex, rh-PDGF-BB.

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1. Introduction

Diabetes is a multisystem disease resulting from altered glycaemic control which affects approximately 3.5% (Type 1: 10%; Type 2: 90%) of the North American population [1]. However, an equal number of people with diabetes remain undiagnosed [2-6], and more disturbing, is the recent increased incidence of this disease amongst children and adolescents. Diabetics face lifelong intensive medical therapy to maintain optimal metabolic homeostasis in the hope of reducing the risk of developing long-term complications associated with this disease [7-9].

Diabetes can lead to a multitude of end organ effects specifically retinopathy, neuropathy, vasculopathy and peripheral neuropathy. Chronic foot problems are a major source of disability, morbidity and mortality amongst diabetics, accounting for a large portion of the financial burden resulting from this condition and frequent admission into hospital [3,10,11]. The foot manifestations of diabetes include peripheral neuropa-

thy, ulcerations, neuropathic arthropathy, osteomyelitis and vascular insufficiency [12]. The estimated annual cost of diabetic foot care in the US alone for chronic non-healing ulcers is US$ 1 billion [13-15]. Diabetic foot ulcerations develop as a consequence of peripheral neuropathy (60 - 70%), peripheral vascular disease (15 - 20%), or due to a combination of neuroischemic changes (15 - 20%) [16-18]. Infection together with excessive and repetitive mechanical stresses may further complicate the underlying foot ulcer. It has been reported that 70 - 90% of neuropathic ulcerations occur in the forefoot with the heel being the next most frequently affected area, followed by the midfoot [12]. Several classification systems have been proposed to aid in the diagnosis and management of foot ulcerations, including the Wagner Classification system [19] and the Depth-Ischaemia Classification system (Brodsky Classification) [20]. Despite efforts to ensure an optimal micro and macro wound healing environment, the diabetic foot ulceration may resist resolution, necessitating the need to consider adjunctive healing measures. These measures range from footwear modifications to corrective surgery in order to address structural and morphologic changes. Conservative techniques such as total contact casting [21] are also of benefit. The techniques used to optimise healing of diabetic foot ulcerations include debriding callus and necrotic debris, ensuring that infection is controlled and optimally displacing weight from the affected area [22].

Approximately 20% of all diabetics who develop lower extremity ulcers will, unfortunately, ultimately require lower extremity amputation. It has been speculated that up to 85% of lower extremity amputations in people with diabetes can be prevented with improved patient foot care education, more effective treatment of diabetic foot ulcerations and better prevention of ulcer recurrence [23].

Becaplermin or recombinant platelet derived growth factor (rh-PDGF-BB) is a new adjunctive therapy for wound healing which has been extensively evaluated for the management of diabetic foot ulcerations. In this article the preclinical and clinical aspects of becaplermin will be considered both in terms of its role as a modulator of wound healing and in particular, its role in the management of diabetic foot ulcerations.

2. Wound healing and platelet derived growth factor

Wound healing is a dynamic process, characterised by three discrete but overlapping stages:

- inflammation
- proliferation and repair
- remodelling

The goal of wound healing is to re-establish sustained anatomic and functional integrity. Numerous factors may negatively influence the primary healing process including [23,24]:

- unrelieved pressure or ongoing trauma (pressure, sheer, friction, repetitive injury)
- ischaemia
- infection (skin, soft tissue, bone)
- inflammatory disorders (vasculitis)
- malignancy (primary and metastatic cutaneous neoplasms)
- haematological abnormalities (hypercoagulable states)
- vascular (venous) and lymphatic insufficiency
- metabolic (diabetes mellitus, renal failure)
- malnutrition (protein, calorie, vitamin)
- immune suppression (chemotherapy, corticosteroids)

In the event that the macro and micro wound environment are not optimal for primary healing, a chronic wound may develop. Unlike the acute wound, chronic wounds heal by secondary intention, this is characterised by an intense inflammatory reaction, large amounts of granulation tissue and most importantly wound or scar contraction.

Wound healing is a complex process co-ordinated by numerous growth factors arising from different cells. These growth factors target specific cells to undertake defined activities (**Table 1**) [24-29]. It has been hypothesised that wounds fail to heal because of the sub-optimal activity of critical growth factors. This can be due to either decreased levels of particular growth factors or the presence of inhibitory factors in the microenvironment [24,25,30-33].

Numerous *in vitro* studies have demonstrated that PDGF plays an important role all stages of the wound healing cascade. Despite the stage dependent, heterogeneous cellular environment that characterises the various stages of wound healing, PDGF is synthesised in significant quantities throughout the process by a number of different cells, including platelets, macrophages, fibroblasts and endothelial cells (**Table 1**). Despite the critical role other growth factors involved in wound healing (EGF, FGF, insulin-like growth factor [IGF] and the TGFs) play in wound healing, only PDGF has been shown to augment wound healing *in vivo* [22].

The molecular makeup of PDGF synthesised by platelets has been elucidated. PDGF exists as a dimer consisting of A and/or B chains held together by a disulfide bond. Three different PDGF isomers have been isolated from human platelets - AA, BB and AB [25,34], the most potent isomer is BB [34,35].

PDGF binds to a cell surface receptor, and two cell surface PDGF receptors have been identified to date. The α-PDGF receptor is non-specific and binds all isoforms of PDGF, while the β-PDGF receptor recognises and selectively binds only the PDGF-BB isoform. The latter is the most common type found on the cell surface [36,37]. Therefore, only the PDGF-BB isomer has been aggressively explored as a potential adjuvant to aid in the healing of chronic wounds.

3. Chemistry

Utilising recombinant DNA technology, a homodimeric protein was produced by inserting the gene for the β chain of human PDGF into the yeast *S. cerevisiae*. The resultant rh-

Tabl 1. Growth factors involved in wound healing.

Growth Factor	Source	Target cells and activity
Epidermal growth factor (EGF)	Platelets, keratinocytes and body fluid	Mitogenic for endothelial cells, keratinocytes, epithelial tissues and fibroblast.
Fibroblast growth factor (FGF)	Macrophages, endothelial cells, osteocytes, smooth muscle, fibroblasts and astrocytes	Endothelial cell growth, mitogen for mesenchymal and neural tissue
Insulin-like growth factor (IGF)	Fibroblasts, macrophages and most other tissues	Mitogenic for fibroblasts, osteocytes, neural tissues, smooth muscle cells, chondrocytes and haematopoietic cells
Platelet derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, fibroblasts and keratinocytes	Chemoattraction of neutrophils and fibroblasts, mitogenic for smooth muscle and fibroblasts
Transforming growth factor-β1 and -β2, (TGF-β1, β2)	Platelets and macrophages	Chemotactic for macrophages and fibroblasts, keratinocyte migration, extra cellular matrix synthesis and remodelling
Transforming growth Factor-β3 (TGF-β3)	Macrophages	Inhibits scar tissue
Vascular endothelial growth factor (VEGF)	Keratinocytes and macrophages	Angiogenesis

Modified from reference [29].

PDGF-BB or becaplermin possesses biological activity similar to that of endogenous PDGF-BB, thus promoting chemotactic recruitment and proliferation of cells involved in the wound-healing cascade [34-37].

4. Animal studies

rh-PDGF-BB has undergone extensive investigation in numerous animal studies and has been shown to enhance the formation of granulation tissue. However, rh-PDGF-BB has variable effects on epithelialisation and wound contracture. Ultimately, all chronic wounds in the animal studies healed.

A study where a single dose of PDGF was applied topically to experimentally introduced incisional skin wounds in rats demonstrated that PDGF improved both the breaking strength of the wounds and accelerated wound healing [38]. However, by 3 months there was no difference in wound healing between those wounds treated with topical PDGF *versus* the wounds treated with a topical placebo. Microscopic examination of the wounds treated with topical PDGF showed a marked increased intensity of the inflammatory phase of the wound healing cascade, characterised by an increased presence of neutrophils, monocytes and fibroblasts. Grossly, this was correlated with an increased production of granulation tissue. Despite the lack of *in vitro* experimental evidence to support a direct effect of PDGF on keratinocytes, rh-PDGF has been shown to increase the rate of epithelialisation in animal incisional skin wound models. It has been suggested that rh-PDGF may influence epithelialisation indirectly through macrophages and fibroblasts, which it attracts to the site of injury [39]. Furthermore, the topical application of rh-PDGF to an incisional skin wounds in animals results in increased neovascularisation of the wound. Biochemical studies have clearly shown that PDGF does not directly stimulate or augment the activity of endothelial cells. It is hypothesised that PDGF positively promotes angiogenesis indirectly through its activities on other inflammatory cells [38,40-44]. Similar results have been reported in the rabbit ear excisional wound model [45]. These promising results of the wound healing activity of rh-PDGF in the animal studies led to clinical trials in order to evaluate the safety and efficacy of rh-PDGF-BB in humans.

5. Studies in humans

The safety and efficacy of rh-PDGF-BB in healing foot ulcerations in diabetics has been studied in several clinical trials, which are summarised in Table 2. In all studies, the patient inclusion criteria included:

- Chronic foot lesion (≥ 8 weeks).
- Adequate circulation (transcutaneous partial pressure of oxygen ($TcPO_2$) ≥ 30 mmHg or ankle-brachial blood pressure index > 0.70).
- The lesion had to be free from infection (superficial skin/soft tissue or bone).

The chronology of the human studies and the results are summarised in Table 2.

A randomised, prospective, double-blind trial to evaluate the safety and efficacy of rh-PDGF-BB to heal neuropathic foot ulcers in diabetics was undertaken [17]. Over the 20-week study period 48% (29/61) of the chronic ulcers healed using topical application of rh-PDGF-BB as opposed to 25% (14/57) of the placebo (vehicle) treated group ($p = 0.01$). The median reduction in the wound area was 98.8% in the rh-PDGF-BB group compared with only 82.1% for those treated with the vehicle alone. It was concluded from this

Table 2. Summary of patient and wound characteristics for becaplermin clinical trials.

		Study 1 (n = 118) [17]		Study 2 (n = 382) [46]		
Study type		Phase II Safety and efficacy		Phase III Safety and efficacy		
Study design		Randomised, double-blind, placebo controlled		Randomised, double-blind, placebo controlled		
Treatment groups		Placebo gel (n = 57)	Becaplermin 30 µg/g (n = 61)	Placebo gel & good ulcer care (n = 127)	Becaplermin 30 µg/g[C] (n = 132)	Becaplermin 100 µg/g (n = 123)
Mean age in years (SD)		58 (11.9)	63 (11.1)	58 (11.8)	58 (11.3)	57 (11.5)
Sex (% of n)	Male	46 (80.7)	43 (70.5)	91 (71.7)	82 (62.1)	82 (66.7)
	Female	11 (19.3)	18 (29.5)	36 (28.3)	50 (37.9)	41 (33.3)
Race (% of n)	White	49 (86.0)	53 (86.9)	100 (78.7)	108 (81.8)	101 (82.1)
	Non-white	8 (14.0)	8 (13.1)	27 (21.3)	24 (18.2)	22 (17.9)
Target ulcer, mean duration weeks (SD)		77 (81.6)	84 (117.9)	46 (52.1)	56 (80.3)	46 (54.7)
Ulcer area[A] cm^2 (SD)		9.0 (16.0)	5.5 (8.5)	2.8 (4.1)	2.6 (2.7)	2.6 (3.4)
Complete closure at 20 weeks (% of n)		14 (25)	29 (48)	44 (35)	48 (36)	61 (50)
Mean days to ulcer closure[B]		NR	NR	127	NR	86

Table 2 has been modified from reference [29]. A: Ulcer area: length x width; B: Mean days to ulcer closure, for those ulcers which healed study 5 (estimated at the 35th percentile in studies 2 and 3); C: Becaplermin 100 mg/g = 0.01% Regranex gel; NR: Not reported; SD: Standard deviation.

study that rh-PDGF-BB gel applied topically once daily was safe and effective for stimulating the healing of chronic, full thickness ulcerations in the lower extremities of diabetics [17].

A subsequent Phase III randomised placebo-controlled double-blind study compared the safety and efficacy of using placebo *versus* rh-PDGF-BB gel 30 µg/g *versus* rh-PDGF-BB gel 100 µg/g [46], where there were 127, 132 and 123 patients in each group, respectively. A significant difference was observed in the incidence of complete healing for 49.5% (61/123) of those receiving 100 µg/g rh-PDGF-BB gel compared to 36.3% (48/132) of those receiving 30 µg/g rh-PDGF-BB gel and 34.6% (44/127) receiving topical placebo gel and good ulcer care, respectively. A significant difference was observed ($p = 0.007$) when comparing the rh-PDGF-BB 100 µg/g gel treated group to the placebo gel treated group. Not only did the topical application of 100 µg/g rh-PDGF-BB gel increase the incidence of wound healing, it also accelerated the time to healing compared to the placebo treated group ($p = 0.013$), 86 and 127 days, respectively. This study demonstrated that rh-PDGF-BB 100 µg/g when combined with good wound care, significantly increased the number of lesions healed and decreased the time to complete wound closure [46].

In another protocol (randomised, double-blind/evaluator-blind placebo-controlled trial), three treatment regimens were compared [47]. A comparison of good wound care alone (n = 68); topically applied sodium carboxymethylcellulose (NaCMC) gel (n = 70); and good wound care plus the topical application of rh-PDGF-BB gel 100 µg/g (n = 34) were undertaken. This study was not powered for statistical analysis, however, it was noted that the individuals in the rh-PDGF-BB 100 µg/g treated group had the highest incidence of healing (44.1%) by 20 weeks. This was compared to 22% for the good wound care alone group and 35.7% for the NaCMC gel treated group [47].

A randomised evaluator-blind controlled trial designed to assess resource use has been presented as part of other reports, although a final summary has not been published. In this study, the incidence of complete ulcer healing in the 100 µg/g becaplermin gel group (35.9%) and the good ulcer care only group (31.9%) were not statistically different. The authors report that physician and patient non-compliance with the study protocol

Table 2. Summary of patient and wound characteristics for becaplermin clinical trial *(continued)*.

		Study 3 (n = 172) [47]			Study 4 (n = 250) [48,49]		Study 5 (n = 134) [50]
Study type		Safety and efficacy and placebo (vehicle) effect			Resource utilisation		Phase IIIb Safety and efficacy
Study design		Randomised, double-blind/evaluator blind, placebo controlled			Randomised, evaluator-blind, placebo controlled		Open label
Treatment groups		Good ulcer care alone (n = 68)	Placebo gel (n = 70)	Becaplermin100 µg/g (n = 34)	Good ulcer care (n = 122)	Becaplermin 100 µg/g (n = 128)	Becaplermin 100 µg/g (n = 134)
Mean age in years (SD)		60 (11.3)	57 (13.0)	59 (11.9)	60 (11.9)	59 (10.8)	60 (12.7)
Sex (% of n)	Male	54 (79.4)	49 (70.0)	24 (70.6)	87 (71.3)	91 (71.1)	95 (70.9)
	Female	14 (20.6)	21 (30.0)	10 (29.4)	35 (28.7)	37 (28.9)	39 (29.1)
Race (% of n)	White	55 (80.9)	63 (90.0)	28 (82.4)	97 (79.5)	104 (81.3)	129 (96.3)
	Non-white	13 (19.1)	7 (10.0)	6 (17.6)	25 (20.5)	25 (18.7)	5 (3.7)
Target ulcer, mean duration weeks (SD)		42 (42.0)	53 (60.9)	20 (14.4)	82 (156.6)	59 (72.4)	80.5 (108.8)
Ulcer area[A] (SD) cm^2		2.5 (2.3)	2.2 (2.2)	1.6 (1.4)	2.5 (3.8)	3.2 (4.7)	2.7 (2.3)
Complete closure at 20 weeks (% of n)		15 (22)	25 (36)	15 (44)	39 (32)	46 (36)	77 (57)
Mean days to ulcer closure[B]		141	98	85	NR	NR	63

Table 2 has been modified from reference [29]. [A]: Ulcer area: length x width; [B]: Mean days to ulcer closure, for those ulcers which healed study 5 (estimated at the 35th percentile in studies 2 and 3); [C]: Becaplermin 100 mg/g = 0.01% Regranex gel; NR: Not reported; SD: Standard deviation.

may be higher with this study protocol than other studies with this therapy. This may have accounted for the lack of statistical significance between the two groups for healing [48,49].

A multi-centre Phase IIIB open label study evaluating the safety and efficacy of becaplermin 100 µg/g when applied in a once-daily regimen (standardised for body weight) was recently reported [50]. In this study, it was observed that 57.5% (77/134) of ulcerations completely healed in the study subjects with a mean time to closure of 63 days and a recurrence rate of 21% at 6 months. Of the potential factors affecting ulcer healing, compliance with study drug ($p < 0.001$), compliance with dressings ($p < 0.01$), presence of infection ($p < 0.01$) and baseline ulcer area ($p < 0.05$) were significantly associated with healing. Results of this study, further confirm the efficacy and safety of becaplermin gel for the treatment of lower extremity diabetic ulcers [50].

In all studies in which becaplermin gel was compared to placebo, the safety profile was comparable for both groups.

A meta-analysis was undertaken to evaluate the treatment of the 922 patients previously reported and the patients from the clinical trial that was not reported [49]. The rationale for the meta-analytic statistical techniques was to appropriately assess efficacy across the four studies. A key step in the process of showing efficacy was the assessment of homogeneity of responses among the treatment groups across the studies for the results for patients with baseline ulcer area < 10 cm^2 (874/922, 95%). Further analysis by logistic regression modelling showed that the use of becaplermin gel 10 0µg/g significantly increased ($p = 0.007$) the probability of complete healing compared with placebo gel. Becaplermin gel 100 µg/g significantly decreased ($p = 0.01$) the time to complete healing when compared to placebo gel. The adverse events experienced for both the becaplermin gel group and those treated with placebo were comparable.

In another recent meta-analysis [51], it was shown that the weighted mean healing rate of 30.9% was achieved at the 20-week time point in the control arms of several clinical trials for

the treatment of lower extremity diabetic ulcerations. In another retrospective study, the 20-week instance of healing was 39.8% for Wagner grade I and II lesions treated with good wound care alone; none of the grade II lesions in this study involved bone [52]. Formal cost analysis for the most of the available therapies for the healing of diabetic foot ulcerations is not available. In a recent cost effectiveness analysis, however, it was observed that becaplermin provided improved healing rates when compared to standard therapy and was less expensive then some of the alternative therapies [53]. These findings, in conjunction with the clinical trial results, highlight the potential benefits of using becaplermin gel to maximise the chances of having lower extremity ulcerations in the feet of diabetics heal.

6. Treatment

rh-PDGF-BB gel may successfully augment the healing of a chronic, diabetic foot ulceration, if used under ideal macro and micro environmental conditions. Ideally, this includes a moist wound healing environment, debridement of all necrotic debris and callus ensuring the area is free of infection and displacement of weight from the affected area. A significant contributor to achieving an optimal wound healing environment is debridement of the chronic wound. Numerous debridement techniques exist including; sharp, mechanical (wet to dry dressings), enzymatic and rarely, the use of maggots. The most effective debridement technique ensures removal of devitalised and dead tissue and subsequent bleeding at the site. It is the induction of a bleeding surface, which initiates the wound-healing cascade as the bleeding wound environment promotes the arrival of platelets and ultimately the release of PDGF into the wound.

Ideally, rh-PDGF-BB should be applied to a clean, debrided wound in a thin layer and covered with a moist gauze dressing, combined with weight displacement from the affected area. This ensures an optimal environment in which healing of the ulceration may occur.

7. Conclusion & expert opinion

rh-PDGF-BB has undergone extensive animal and human evaluation, and it is the first commercially available growth factor demonstrating efficacy in the healing of diabetic foot ulcers when used in conjunction with an optimal wound healing environment. Adverse effects have not been reported to date from the topical application of rh-PDGF-BB in humans.

To ensure efficacy and healing of diabetic foot ulcers using rh-PDGF-BB, it is imperative that a thorough assessment of the patient be undertaken to ensure adequate peripheral circulation, the absence of a wound or bone infection and the debridement of necrotic debris and callus from the wound. This will improve the macro and micro wound healing environment and therefore optimise the efficacy of the adjuvant topical application of rh-PDGF-BB.

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